

The Pharmacotherapy of Insomnia: Efficacy and Rebound With Hypnotic Drugs

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© Currently prescribed hypnotics (i.e., benzodiazepines and benzodiazepine-like compounds) are commonly categorized according to pharmacokinetic profile, which is primarily distinguished by long, intermediate, or short elimination half-life. Hypnotics with a long elimination half-life (flurazepam and quazepam) maintain efficacy over prolonged periods of nightly use and their discontinuation does not usually result in rebound insomnia, but they have the major drawback of causing unwanted potent daytime sedative effects. Use of intermediate half-life hypnotics (estazolam, flunitrazepam, lormetazepam, nitrazepam, and temazepam) is associated with carryover effects of moderate intensity and varying degrees of tolerance and rebound insomnia. Rapidly eliminated benzodiazepine (brotizolam, midazolam, triazolam) and nonbenzodiazepine (zaleplon, zolpidem, and zopiclone) hypnotics are practically devoid of carryover effects, making them appropriate for use in the majority of cases of insomnia, but they are generally associated with relatively rapid development of tolerance and rather frequent occurrence of rebound insomnia upon their discontinuation. Contrary to previous beliefs, tolerance and rebound insomnia vary considerably among the rapidly eliminated hypnotics: tolerance is intense with triazolam and slight with midazolam and zolpidem, while rebound insomnia is intense with triazolam, variable with midazolam, and quite mild with zolpidem. For brotizolam, zaleplon, and zopiclone, existing relevant research findings are still inconclusive; brotizolam and zopiclone, however, appear to have a marked potential for the development of tolerance and/or rebound insomnia, which does not seem to be the case with zaleplon.

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Insomnia is usually the outcome of the interplay of various biological and psychological etiologic factors and, therefore, requires a multidimensional therapeutic approach.¹⁻⁹ Consequently, hypnotic drugs should not be the sole treatment modality in the management of insomnia. Rather, they should be generally administered as a part of the overall therapeutic intervention in order to help the patient gain mastery in combating the fear of sleeplessness and facilitate the implementation of psychotherapy and other treatment methods as they may be needed.^{1,5,9}

The drugs currently marketed as hypnotics (Table 1) have a much more favorable side-effect profile and a larger therapeutic margin compared with the barbiturates, which were formerly used in the treatment of insomnia.¹⁰ The benzodiazepine receptor on the γ -aminobutyric acid receptor type A (GABA_A) is the site of action of hypnotic

drugs; binding of the drug to this receptor facilitates the inhibitory action of GABA in the central nervous system (CNS).¹¹ The GABA_A receptor is a multimeric membrane-spanning ion channel consisting of various combinations of more than 15 known subunits,¹² and different drugs are known to bind with varying degree of affinity to different receptor types produced by these combinations.¹³ For example, most benzodiazepines show similar affinity to all types of GABA_A receptors, while the benzodiazepine-like compounds generally differentiate among these types.^{13,14} Additionally, compared with other nonbenzodiazepine hypnotics, zaleplon has a much lower affinity for the target receptor,¹⁴ thereby providing effective sleep induction without significant impairment at peak plasma concentrations.¹⁵

All hypnotic drugs share short absorption and distribution times, which lead to a relatively short period between their intake and highest plasma concentrations. This pharmacokinetic characteristic allows for rapid sleep induction following intake of the drug and is particularly important since delayed sleep onset is often the main complaint of patients with insomnia.¹⁶ However, based on their rate of elimination, hypnotics can be broadly distinguished in 3 categories (see Table 1): those with long elimination half-lives (40–200 hours), those with intermediate elimination half-lives (8–40 hours), and those with short elimination

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Table 1. Currently Available Hypnotics: Broad Categories and Subgroups Based on Elimination Half-Life

Benzodiazepines	Long elimination half-life	Flurazepam
		Quazepam
	Intermediate elimination half-life	Estazolam
		Flunitrazepam
		Lormetazepam
		Nitrazepam
		Temazepam
	Short elimination half-life	Brotizolam
		Midazolam
		Triazolam
Benzodiazepine-like compounds	Short elimination half-life	Zaleplon
		Zolpidem
		Zopiclone

half-lives (1–8 hours).^{17,24} The benzodiazepine hypnotics initially developed had a long elimination half-life; consequently, their administration was associated with carryover effects, such as next-day sleepiness and impaired performance reflected in psychomotor and cognitive impairment.^{25–36} The rapidly eliminated hypnotic drugs, which were developed subsequently, were practically devoid of carryover effects but were found to be associated with earlier and more frequent development of tolerance as well as with more intense rebound insomnia, amnesia, and other behavioral side effects than the slowly eliminated ones.^{37–44}

The present review on efficacy, tolerance, and rebound with hypnotic drugs will be primarily based on sleep laboratory studies. In these studies, the quantification of the sleep parameters is accurate and objective, allowing for the identification of changes that depict initial efficacy, development of tolerance, or presence of any rebound effects. The controlled environment of the sleep laboratory and the strict experimental design provide standardized conditions that make the evaluation of even the subjective variables very reliable.^{45–48} As such, subjective data from clinical trials will be used as appropriate to support findings from sleep laboratory studies.

EFFICACY

Initial Efficacy

All hypnotic drugs have been shown to be initially efficacious for the treatment of insomnia, irrespective of the length of their elimination half-lives.^{41,44,49–54} Hypnotics with long elimination half-lives usually show their highest effectiveness in the second and third night of administration, after the accumulation of the parent drug and its active metabolites is achieved.^{27,55,56} In contrast, the rapidly eliminated hypnotics usually demonstrate effective sleep-inducing effects on the very first night.^{57–60} In fact, zaleplon, which is very rapidly eliminated, can be used as an effective sleep inducer not only at bedtime but also after a prolonged unsuccessful attempt to sleep or even following a disturbing awakening occurring in the first half of the night.^{61,62}

Tolerance

The effectiveness of the slowly eliminated hypnotics, flurazepam and quazepam, is well retained into the third week of their administration.⁴⁴ A slight loss of efficacy with continued use, observed in some studies, is either merely subjective⁶³ or does not reach a magnitude that considerably affects hypnotic potency.^{26–28,44,64,65} For the agents with intermediate elimination half-lives (estazolam, flunitrazepam, lormetazepam, nitrazepam, and temazepam), loss of efficacy with continued use was reported in some studies.^{66–73} In other studies, however, development of tolerance during 2 weeks of nightly administration was not demonstrated with these drugs.^{74–80}

Regarding the rapidly eliminated hypnotics, certain sleep laboratory studies showed clear-cut loss of efficacy 1 to 2 weeks following nightly use.^{1,44,49,57,58,71,81–85} However, the results of other studies did not demonstrate development of tolerance with these drugs.^{51,64,86–95} To resolve this controversy, we recently conducted a meta-analysis of all sleep laboratory studies of 5 hypnotics with short elimination half-lives that were published until 1997 (i.e., brotizolam, midazolam, triazolam, zolpidem, and zopiclone). The results of this meta-analysis showed that tolerance with continued use is intense for triazolam and slight for midazolam and zolpidem. For brotizolam, there were no data allowing any conclusions to be drawn; data pertaining to zopiclone, although inconclusive, provided evidence for development of tolerance with this drug.⁵³

The newly marketed hypnotic zaleplon has been assessed for continued efficacy in 2 sleep laboratory studies on insomniacs who were administered the 10-mg dose for either 2⁴⁹ or 5 weeks.⁵¹ Sleep latency was significantly shorter during initial administration of zaleplon, 10 mg, compared with placebo (by 6.1 min, $p < .04$ in the 2-week study and by 15.7 min, $p < .005$ in the 5-week study); in 1 study, the decrease of sleep latency was not statistically significant in the second (i.e., final) week,⁴⁹ yet in the other study the decrease persisted to a statistically significant degree up to 5 weeks (sleep latency was 8.2 min shorter with zaleplon, 10 mg, than with placebo for weeks 3–5, $p < .05$).⁵¹

REBOUND INSOMNIA

Kales and associates^{42,96,97} termed the worsening of sleep difficulty above baseline levels following withdrawal of a hypnotic *rebound insomnia*. Rebound insomnia does not seem to follow the discontinuation of hypnotics with long elimination half-lives, because the majority of studies of flurazepam and quazepam actually show carryover hypnotic effects during the withdrawal period of these drugs.* A few studies provided evidence of some worsening of

*References 27, 28, 44, 55, 57, 65, 70, 77, 91, and 98–104.

sleep following withdrawal of flurazepam, but this did not appear to have clinical significance, either because it was very mild, delayed, and/or transitional^{26,28} or it was not objectively substantiated in the sleep laboratory.⁶³

Results of studies on discontinuation of hypnotics with intermediate elimination half-lives are variable regarding the propensity of these drugs to cause rebound insomnia. The discontinuation of nitrazepam, estazolam, and lorazepam was followed by development of rebound insomnia in some studies^{66,72,75,77,79}; yet this was not the case in a study of 0.1 mg of lorazepam in the elderly.⁷⁸ Similarly, temazepam, 30 mg, was found to cause rebound insomnia in 3 studies,^{74,76,105} but not in 2 other studies^{84,106}; moreover, doses up to 20 mg were found not to be associated with the development of rebound insomnia.^{70,74,84,107,108} Finally, 2 studies of flunitrazepam showed occurrence of rebound insomnia upon its discontinuation,^{68,109} although in another 5 studies no rebound was evident with this drug.^{67,80,110–112}

Rebound insomnia is considered to be the main drawback of the rapidly eliminated hypnotics.^{37,42,43,52,96,97} Until recently, a controversy existed on whether the frequency and intensity of rebound insomnia substantially differ across these agents.^{44,113–117} This controversy was addressed through a meta-analysis conducted on all published studies of brotizolam, midazolam, triazolam, zopiclone, and zolpidem.⁵³ Results of this meta-analysis showed that when the first withdrawal night is compared with baseline, the discontinuation of triazolam causes an average decrease in total sleep time of more than 1 hour and an increase in sleep onset latency of about 30 minutes. On the contrary, the discontinuation of zolpidem was found to cause a milder degree of rebound insomnia on the first withdrawal night, with sleep latency being on average 13 minutes longer than at baseline.⁵³ Mean values from individual studies of brotizolam and midazolam (for which data were inadequate for the meta-analysis) suggested that discontinuation of these drugs may cause variable degrees of rebound insomnia.^{53,90,118} Although data pertaining to the withdrawal period of zopiclone were also inadequate for the meta-analysis, there is some evidence that discontinuation of this drug may result in rebound insomnia.^{53,94} Zaleplon was not marketed until 1999 and was thus not included in the meta-analysis. However, the results of 2 sleep laboratory studies^{49,51} have been corroborated by subjective reports in 3 clinical studies,^{119–121} indicating that rebound insomnia does not seem to be a significant consequence of the discontinuation of zaleplon.

CLINICAL IMPLICATIONS

Benzodiazepine and benzodiazepine-like hypnotics can be placed in 3 categories according to their pharmacokinetic characteristics. Flurazepam and quazepam have a long elimination half-life; estazolam, flunitrazepam, lorazepam, nitrazepam, and temazepam have an interme-

diolate elimination half-life; and brotizolam, midazolam, triazolam, zaleplon, zolpidem, and zopiclone have a short elimination half-life.^{17–24} All these hypnotics are initially efficacious, especially in terms of reduction of sleep onset latency following their administration.^{27,41,44,49–56} Nonetheless, development of tolerance, occurrence of rebound insomnia, and presence of residual sedation or other behavioral side effects are clinical characteristics that distinguish among them^{37–44} and should be taken into account when considering their prescription.

Hypnotics with long elimination half-lives are not characterized by early development of tolerance, and their use is not associated with the occurrence of rebound insomnia upon their discontinuation.* They have, however, the disadvantage of unwanted carryover effects, i.e., daytime somnolence and marked psychomotor and cognitive impairment,^{25–36} which render them inappropriate for use in the majority of patients with insomnia. The intermediate half-life hypnotics generally present with milder carryover effects than the slowly eliminated ones^{31,66,68,122–131} and a relatively moderate degree of tolerance and rebound insomnia.^{66–80,84,105–112}

The main advantage of the rapidly eliminated hypnotics is that their use is practically devoid of residual sedation or next-day psychomotor impairment.^{29,32,34,126,132–134} On the other hand, tolerance may develop even after the first week of nightly administration,^{1,44,49,53,57,58,71,81–85} and rebound insomnia is not an unusual occurrence upon discontinuation.^{37,42,43,52,53,90,94,96,97,118} Elimination half-life, however, is not the only pharmacologic characteristic leading to the development of tolerance and rebound insomnia, both of which seem to be dependent on other properties of these drugs, such as binding affinity and receptor binding site specificity.^{17,135} For example, tolerance has been shown to be relatively intense with triazolam and slight with midazolam and zolpidem, while rebound insomnia was found to be quite intense with triazolam and rather mild with zolpidem.⁵³ For brotizolam, zaleplon, and zopiclone—the 3 other rapidly eliminated hypnotics—existing data are still inconclusive; brotizolam and zopiclone, however, may have marked propensity for the development of tolerance and/or rebound insomnia, which does not seem to be the case with zaleplon.^{49,51,53,90,94,119–121}

CONCLUSION

From a practical standpoint, the following clinical recommendations can be offered for the use of hypnotics in the management of insomnia. Because unimpaired next-day performance is desirable for patients with insomnia, a rapidly eliminated hypnotic is usually appropriate as part

*References 26–28, 44, 55, 57, 63–65, 70, 77, 91, 98–101, 103, and 104.

of a multidimensional treatment approach. Individual characteristics of hypnotic drugs, such as propensity for the development of tolerance with prolonged use and occurrence of rebound insomnia upon discontinuation, invariably should be taken into consideration.

Drug names: estazolam (ProSom and others), midazolam (Versed), quazepam (Doral), temazepam (Restoril and others), triazolam (Halcion), zaleplon (Sonata), zolpidem (Ambien).

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